the implementation of the ideology of antibiotic policy, stressing the unique role of antibiotics.

Pathogenesis and prevention of polymer-associated staphylococcal infections

S76 Overview of the clinical presentation and problems of polymer-associated staphylococcal infections, with special emphasis on catheter-related infections

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Polymer-associated infections of staphylococci are, in the majority of cases, caused by coagulase-negative staphylococcl (CNS) and include infections associated with a wide variety of indwelling devices, from intravascular catheters to joint and cardiac valve prostheses to cerebrospinal fluid shunts and devices used for peritoneal dialysis. Infection is one of the commonest and most serious complications of indwelling devices. The clinical presentation varies greatly, and diagnosis may either be straightforward or extremely difficult. Usually there is an indolent clinical picture with low-grade fever and minimal local signs of inflammation, e.g. in cases of intravascular catheter-related infections or prosthetic joint infections. However, in some cases of prosthetic valve endocarditis, there may be a life-threatening course characterized by a sudden onset with high fever and chills and severe dysfunction of the prosthetic valve. The difficulties in diagnosis of the usual case with an indolent course with minimal clinical signs are particularly well illustrated by many cases of intravascular catheter-related infection. This had led to numerous attempts to provide accurate clinical and microbiological criteria to establish the diagnosis of catheter-related infection, with more or less success. Some criteria are, for obvious reasons, not easily applicable to certain patient categories e.g. multiple blood cultures in premature neonates. Others, notably some of the proposed microbiological criteria, require methods that are too cumbersome and time-consuming for a routine clinical laboratory.

A keen clinical eye remains, more often than not, the most helpful instrument for the initial diagnosis; the published clinical criteria may aid, together with some of the more advanced microbiological methods and scanning techniques, in finally establishing the diagnosis of a device-related infection.

S77 Recent insights into molecular pathogenesis

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Staphylococci may colonize foreign material by any of three routes: (1) prior to insertion through the surgical wound; (2) after insertion through catheter hubs or skin wounds; or (3) hematogeneously. Consequently, for initial adhesion to the foreign surface, staphylococci have to interact either with native or with host factor-adsorbed polymer. Both *Staphylococcus aureus* and coagulase-negative staphylococci (CNS) have been shown to avidly interact with proteinaceous host factors such as fibronectin and fibrinogen. A number of bacterial adhesins have been implicated in this adhesion process, and the role of some of these adhesins has been molecularly characterized. In addition to plasma factors, *S. aureus* binds to surface-adsorbed blood platelets and their membrane-exposed granule contents such as thrombospondin or von Willebrand factor (vWF). Molecular analysis indicates a role of two fibrinogen-binding adhesins, i.e. Coa/FbpA and Efb, in platelet binding, and of protein A in vWF binding. Adhesion of CNS to native polymer is mediated by an autolysin, AtlE, which influences bacterial surface characteristics and binds to plasma proteins such as vitronectin. After initial adhesion, staphylococci may accumulate on the surface, resulting in biofilm formation. Products of the recently identified *icaADBC* gene cluster in CNS confer production of polymerized polysaccharide antigens such as PIA and PS/A, are involved in phase variation and are associated with clinical disease. Furthermore, biofilm formation requires expression of an accumulation-associated protein, AAP. In summary, a number of molecularly characterized mechanisms contribute to the ability of staphylococci to colonize and infect foreign material. Future research activities may be directed towards enhanced understanding of the respective role and regulation of these mechanisms under the complex conditions present in vivo.

S78 Lessons learned from animal models and from use in humans

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Microbial adhesion to foreign material is an initial and fundamental mechanism for the development of infection. On their surfaces, staphylococci, in particular *Staphylococcus aureus*, express several receptors or adhesins which interact with specific host proteins such as fibrinogen, fibronectin, collagen, vitronectin, laminin, thrombospondin, bone sialoprotein, or elastin. Information on the molecular structure of *S. aureus* genes coding for bacterial adhesins is growing rapidly. Cloning, sequencing and site-directed mutagenesis of the corresponding genes for major *S. aureus* adhesins have allowed the characterization of the molecular structure and function of one fibrinogen-binding protein (=clumping factor), one collagen adhesin, and two distinct but related fibronectin-binding proteins.

Site-specific mutants of each individual adhesin showed specific defects in adhesion to their respective host proteins. Furthermore, adhesion-defective mutants complemented with functional genes (located either on multicopy plasmids or integrated into the bacterial chromosome) allowed full restoration of each adhesion phenotype. The ligand-binding domains of either fibronectin, fibrinogen or collagen adhesins have been identified by binding and inhibition studies performed with recombinant truncated protein fragments or synthetic peptides. Animal models of endocarditis and bioimplants have shown that mutants of *S. aureus* defective in either a fibronectin or a fibrinogen adhesin have less ability to attach and to induce experimental infection. Elucidation of molecular mechanisms of bacterial attachment to host tissues and biomedical implants as well as invasion of non-phagocytic cells may lead to the development of better therapeutic approaches for *S. aureus* infections.

Clinical impact of new diagnostic methods in microbiology

S80 New automated systems for identification and antibiotic resistance detection

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Automation of the bacteriology laboratory has not yet become a reality. However, new instruments such as the VITEK 2 have recently

become available and bring us a step closer to rapid results produced by real automatic equipment with an absolute minimum of hands-on time. An increasing number of publications confirm the excellent performance of this new instrument, not only for the identification of microorganisms, but particularly for susceptibility testing. The new concept comprises the determination of a enlarged range of MICs which are then analyzed by the antimicrobial expert system which has been designed and is continuously updated by a widely accepted international panel of experts. This approach takes us a step further from simple susceptibility testing using breakpoints and closer to the oriented detection of antimicrobial resistance mechanisms, useful recommendations and closer collaboration between clinicians and microbiologists. The impact on the management of patients and on therapy has not yet been fully evaluated. In the view of worldwide cost constraints, restriction of hospital beds, shorter hospitalization time and shift to ambulatory medicine, it can be expected that more rapid and complete results will be a cornerstone of cost-efficiency. Some reorganizations of the microbiology laboratory will be necessary to optimize the possibilities offered by the VITEK 2. They adapt well to the increasing expectation of our technicians to work part-time, the extension of opening hours of laboratories and the streamlining of workflow in merging laboratories.

S81 Surveillance of antibiotic resistance: expert systems and surveillance networks

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The importance of antibiotic resistance surveillance is now recognized. It helps to control infections, to establish empirical antibiotic therapy protocols and to implement a policy of antibiotic usage. An effective surveillance system relies on the combination of an information system, automation and the ability to transfer data to other sites. A surveillance system should produce results leading to rapid and appropriate information and action. Whereas standard laboratory methods measure susceptibility or resistance to individual antimicrobials, most expert systems allow us to characterize in addition the resistance phenotypes of organisms and thus to infer resistance mechanisms. This in turn gives rise to better identification of epidemic strains or epidemic resistance mechanisms and therefore allows us to implement early infection control measures. Expert systems can also generate computer alerts, which play an important role in the early prevention of resistant organism transmission. The interest in expert systems is not limited to local surveillance and intervention but extends to national or global networks of antibiotic resistance. These networks should be supplied with homogeneous data resulting from standardized techniques. Combination of automation and expert systems tends to satisfy this requirement, since it yields reproducible and repeatable results. Finally, the use of quantitative rather than qualitative data is an additional feature of certain systems.

S82 Molecular methods for diagnostic microbiology: current and future trends

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The next generation of molecular diagnostic tests for cancer, infectious diseases and genetic predisposition will depend on multilocus genetic analysis, often involving analysis of highly complex targets or mixtures of targets. Driven in part by the expansion of the worldwide human genome projects, advances in DNA sequencing technology have resulted in systems that are easier to use and operate, at ever-decreasing cost. Genetic array technology is well suited to complex genetic analysis because of its ability to carry out multiple types of reactions, including DNA sequencing and quantitative mRNA expression analysis. This presentation will provide some examples of new molecular diagnostic paradigms that involve DNA sequencing and array-based procedures, including the identification and typing of microbes, evaluation of genetic predisposition to unusual outcomes of chronic infections, and the use of gene expression patterns to classify disease states.

S83 Influence of new diagnostic methods on clinical practice

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Currently there are major shortcomings in the laboratory definition of infection. Few community-managed infections are diagnosed with sufficient accuracy to impact on management and, in turn, to provide a more complete picture of the true epidemiology of infectious disease for the purposes of healthcare planning. Even among hospitalized patients, many infections remain undocumented or, when defined, the management of only a minority is influenced significantly. To impact on disease management more effectively, ideally new technologies should be available at the point of medical consultation, discriminate between infecting and colonizing pathogens, aid therapeutic management in a timely manner and, of course, be affordable! Rapid culture-based diagnostics will partly address these issues. However, molecular-based diagnostics have the potential for greater impact, particularly if they are specimen based and not reliant on pure culture. The clinical features of many acute infections are not sufficiently discriminating to define etiology. Thus chip technology directed at syndromes such as UTI, LRTI, URTIE, STD, SSTI, meningitis and 'jaundice' could have a major impact on disease definition and management. However, they will require new thinking with regard to the definitions of disease and endpoints of response. The future will be very interesting.

Respiratory infections: strategies for a resistance environment

S84 The resistance environment: a view from the Alexander Project

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Resistance mechanisms have emerged against all classes of antibiotics so, in the absence of novel agents, it is important that the right antibiotics are used to obtain the optimal treatment outcome, while minimizing the impact of resistance. High-quality surveillance programs, such as the Alexander Project, are necessary to monitor the prevalence of resistance and guide clinicians in their treatment choices.

Resistance in *Streptococcus pneumoniae* has become a global concern in recent years. The Alexander Project reports a high prevalence of penicillin resistance in many regions, particularly in Spain, France, Mexico, the USA and Hong Kong. The trend of resistance is upwards, even in regions where resistance has been low, such as the UK, Germany and other northern European countries. The prevalence of macrolide resistance is also increasing dramatically, and has reached significant levels (20%+) in many areas, and exceptionally high levels in South East Asia (almost 80% in Hong Kong). The prevalence of beta-lactamase-producing strains of *Haemophilus influenzae* has also increased significantly in recent years, but may be leveling off in those